Effects of Intravenous Glucose Load on Insulin Secretion in Patients with Ketosis-Prone Diabetes Mellitus during Near-Normoglycemia Remission

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Short title: β-cell function in KPDM

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**Objective:** Most patients with ketosis-prone type 2 diabetes mellitus (KPDM) discontinue insulin therapy and remain in near-normoglycemic remission. This study aimed to determine the effect of glucotoxicity on β-cell function during remission in obese patients with KPDM.

**Methods.** Age- and BMI-matched obese African-Americans (AA) with history of KPDM (n=8), severe hyperglycemia but without ketosis (ketosis-resistant T2DM, n=7), and obese controls (n=13) underwent intravenous infusion of 10% dextrose at rate 200 mg/m²/min for 20 hours. β-cell function was assessed by changes in insulin and C-peptide concentration during dextrose infusion and by changes in acute insulin response (AIR) and first-phase insulin release (FPIR) to arginine stimulation before and after dextrose infusion.

**Results.** The mean time to discontinue insulin therapy was 7.1±1.7 weeks in KPDM and 9.6±2.3 weeks in ketosis-resistant T2DM, p=NS. During 20-hr dextrose infusion, changes in insulin, C-peptide and C-peptide/glucose ratio were similar among diabetic and control groups. During dextrose infusion ketosis-resistant T2DM had greater area under curve for blood glucose than KPDM and control subjects, p<0.05. The AIR and FPIR to arginine stimulation as well as glucose potentiation to arginine assessed before and after dextrose infusion were not different among study groups.

**Conclusions.** Near-normoglycemia remission in obese AA patients with KPDM and ketosis-resistant T2DM is associated with a remarkable recovery in basal and stimulated insulin secretion. At near-normoglycemia remission, KPDM patients displayed a pattern of insulin secretion similar to ketosis-resistant T2DM and obese nondiabetic subjects.
The majority of obese African-American (AA) patients with newly diagnosed diabetes mellitus presenting with unprovoked diabetic ketoacidosis (DKA) display clinical and metabolic features of type 2 diabetes mellitus (T2DM) during follow up and are able to maintain near-normoglycemic remission from several months to years without insulin or oral agents (1-7). This variant of T2DM has been referred in the literature as atypical diabetes, type 1B diabetes, and ketosis-prone DM (KPDM) (1; 6). We and others have reported that more than half of KPDM patients, aggressive insulin therapy for ~10 weeks results in significant recovery of β-cell function and in improvement in insulin sensitivity to allow discontinuation of insulin therapy (2; 3; 5; 8-10).

The underlying mechanism for the transient insulin deficiency leading to severe hyperglycemia ketoacidosis in AA with KPDM is unknown. It is possible that sustained hyperglycemia per se before the development of DKA down-regulates the β-cell insulin production capacity. The concepts “glucotoxicity” have been put forward to explain the contribution of toxic effects of hyperglycemia on β-cell function (11). The ability of KPDM patients to be withdrawn from insulin therapy and remain in near-normoglycemic remission suggests hyperglycemia-induced transient β-cell dysfunction. However, it is unknown exactly how the β-cells respond to hyperglycemia and whether KPDM patients during the near-normoglycemia remission phase will display deterioration of insulin secretion after a sustained glucose challenge. In this study, we hypothesized that, compared to obese T2DM patients with hyperglycemia and obese non-diabetic control subjects, obese AA with KPDM during near-normoglycemia remission will experience diminished insulin response to sustained elevations in blood glucose or β-cell glucotoxicity. All subjects underwent a 20-hour infusion of dextrose solution with serial measurements of insulin, C-peptide, and BG and sequential arginine stimulation test before and after dextrose infusion.

RESEARCH DESIGN AND METHODS:
Study Subjects and Controls. A group of 8 newly diagnosed obese (BMI > 30 kg/m²) AA patients with a history of unprovoked DKA, 7 patients with ketosis-resistant T2DM, and 13 obese non-diabetic controls participated in this study. The diagnosis of DKA was established by standard ADA criteria (12). The ketosis-resistant T2DM group included patients with recently diagnosed diabetes with BG>400 mg/dL but without metabolic acidosis or ketosis. The control nondiabetic group included obese subjects, matched for age and BMI, with a fasting glucose < 100 mg/dL and a 2-hour glucose <140 mg/dL during a (75 g) oral glucose tolerance test. This study was conducted at the Clinical Research Center at Grady Memorial Hospital (GMH), Atlanta, GA and was approved by Emory University Institutional Review Board.

At presentation, diabetic patients with DKA and hyperglycemia were treated with a low-dose intravenous insulin infusion protocol (12). After resolution of ketoacidosis and/or hyperglycemia, patients were treated with NPH and regular insulin twice daily at a starting dose of 0.8 units/kg of body weight and weaned per our previously described protocol (13).

Experimental Procedures:
Near-normoglycemia remission was defined as the ability to discontinue insulin therapy for > 1 week and remaining in good glycemic control (fasting BG < 130 mg/dL, random BG < 180 mg/dL, and A1C < 7%). Diabetic subjects were admitted to the GMH Research Center ≥ 1 week after discontinuation of insulin therapy. After an overnight fast, an intravenous catheter was
placed in each forearm, one for infusion and one for blood sampling.

**Twenty hours dextrose infusion protocol.** An infusion of 10% dextrose with 5 mEq/L of KCl was administered for 20 hours at 200 mg/m²/min. The administration of dextrose at this rate has been shown to result in mild to moderate elevation in BG levels in controlled studies (14). During dextrose infusion, blood samples were also drawn every 60 minutes for the determination of insulin and C-peptide and every four hours for measurement of free fatty acids (FFAs). The glucose infusion started at 12:00 noon and continued until 08:00 next morning. Subjects consumed a 2000 cal/day isocaloric diet (20% of calories derived from protein, 30% from fat, and 50% from carbohydrate) served before dextrose infusion and at 18:00 hours during glucose infusion.

**Arginine stimulation test.** Arginine stimulation test enables estimations of the β-cell function and the glucose potentiation of insulin secretion (15). Two sequential arginine stimulation tests were performed, the first set prior to and the second after completion of the 20-hour dextrose infusion. Each arginine stimulation test set was performed at baseline and following a 45-min infusion of 10% dextrose at 200 mg/m²/min. A maximally stimulatory dose of 10% arginine (5 g) was injected as a bolus over a period of 30 seconds and blood samples were drawn at −30, 0, and at 2, 3, 4, 5, 7, 15, and 30 min for measurement of glucose and insulin levels.

**Calculations.** Acute insulin response (AIR) to arginine was defined as the difference between basal (-30 and 0 min) and the mean insulin values at 2, 3, 4, and 5 minutes following each arginine pulse at fasting glucose (AIR₁) as well as after 45-min of dextrose infusion at 200 mg/m²/min (AIR₂). First-phase insulin release (FPIR) was calculated as the sum of the insulin levels at 2, 3, 5, and 7 minutes after arginine infusion. Insulin resistance was estimated by homeostasis model assessment of insulin resistance by homeostasis model assessment derived from fasting plasma glucose and insulin (HOMA-IR = fasting insulin (milliunits per liter) x fasting glucose (millimoles per liter)/22.5. We also estimated insulin sensitivity for the level of insulin secretion (HOMA-IR/first-phase insulin response [FPIR]), which is predictive of progression to β-cell failure and to type 1 diabetes (16).

**Laboratory methods.** Plasma glucose was measured using the glucose oxidase method. Levels of insulin, C-peptide, and FFAs, were measured in plasma using a solid phase, two-site sequential chemiluminescent immunometric assays on the DPC Immulite analyzer (Diagnostic Products Corporation, Los Angeles, CA). The instrument calibrations for the assays were performed as recommended by the manufacturers and were within the specifications.

**Statistical analysis.** All data in the text and table are expressed as mean ± standard deviation, and the data in figures are expressed as mean ± standard error. Comparisons among the nondiabetic control group, KPDM group, and obese diabetic group with hyperglycemia were conducted using nonparametric Kruskal-Wallis tests for continuous variables and Fisher’s exact test for categorical variables. Further analysis for statistical difference between groups was performed by ANOVA. With glucose infusion data, repeated measures analyses were carried out to assess the group difference simultaneously with the change over time in blood glucose, insulin, and C-peptide/glucose ratio, adopting AIR₁ within-subject correlation structure. Statistical significance was defined as p<0.05. Statistical analysis was performed using the SAS 9.2 (SAS Institute Inc, Cary, NC).

**RESULTS:**
Patient characteristics. The clinical characteristics of patients with KPDM, ketosis-resistant DM, and non-diabetic controls are shown in Table 1. Age and BMI were similar among study groups. Most patients with KPDM and ketosis-resistant T2DM had a strong family history of DM and were newly diagnosed at presentation and were predominantly males. On admission, the patients with KPDM had a mean BG level of $712\pm342$ mg/dL and had metabolic acidosis. The ketosis-resistant DM patients with hyperglycemia had an admission BG of $492\pm163$ mg/dL but lacked features of metabolic acidosis (Table 1). The mean time to achieve remission and insulin discontinuation was similar in obese KPDM and ketosis-resistant DM patients (Table 1). At remission, both groups of patients with DM had similar glucose and hemoglobin A1C levels.

Metabolic studies and acute insulin response to arginine stimulation. The results of fasting glucose and plasma insulin levels and arginine stimulation tests are shown in Table 2. At near-normoglycemic remission, plasma concentrations of fasting BG, insulin, C-peptide and HOMA-IR values were not significantly different between patients with KPDM and obese nondiabetic control subjects, p=NS. However, patients with ketosis-resistant DM had higher fasting glucose and HOMA-IR compared to control subjects, p<0.05. Fasting FFA levels were not significantly different between diabetics at remission and controls (Table 2).

Acute insulin response (AIR) and first phase insulin release (FPIR) to arginine stimulation was not significantly different in KPDM and ketosis-resistant T2DM compared to control subjects both before and after 20-hour dextrose infusion (Table 2 and Figure 1). Similarly, the FPIR adjusted for insulin sensitivity (HOMA IR-to-FPIR ratio) was similar between groups before and after glucose load (Table 2).

Glucose, insulin, C-peptide/glucose ratio, FFAs during 20-hour dextrose infusion. Dextrose infusion at a rate of 200 mg/m²/min (~ 25 grams of glucose/hour or 250 ml/hr of D10-solution for a 100 kg person) resulted in mild elevation of BG from baseline in both DM and control subjects (Figure 2A). Repeated measures analyses showed that, during the infusion, BG concentration significantly increased over time from baseline in all groups, p<0.05. However, the patients with KPDM had only mild BG elevation during 20-hr dextrose infusion which was similar to the control group; in contrast, the patients with ketosis-resistant DM had greater BG elevation during dextrose infusion compared with the two other groups, p=0.006. The area under curve (AUC) for glucose levels was similar between control and KPDM groups but was significantly greater in obese subjects with ketosis-resistant T2DM group at $2469\pm254$, $2804\pm344$ and $3607\pm254$ mg/dL per 20 hrs, respectively (p=0.002).

All subjects experienced statistically significant increases in insulin concentration and insulin secretion as assessed by C-peptide/glucose ratio during the 20-hour glucose infusion (Fig. 2B and 2C). However, neither KPDM nor ketosis-resistant DM subjects had significant changes in insulin and C-peptide/glucose ratio compared with the control group assessed at most time points (Fig. 2B and 2C) or by AUC, p=NS.

In nondiabetic control patients, dextrose infusion was associated with a significant decrease in FFA levels. Pre-infusion FFA levels (113±21 µmol/l) markedly declined during dextrose infusion to $63\pm8$, $70\pm7$, $56\pm2$, and $42\pm8$ µmol/l at 8, 12, 16, and 20 hours, respectively, p<0.05. In contrast, in KPDM and ketosis-resistant DM groups, levels of FFA did not substantially change from baseline value throughout the 20-hour dextrose infusion, p=NS.
DISCUSSION:

The two major findings in our study are the remarkable recovery of basal and stimulated insulin secretion during the near-normoglycemic remission in newly diagnosed patients with KPDM, and the lack of β-cell failure (glucotoxicity) after short-term intravenous dextrose infusion. Patients with KPDM at near-normoglycemia remission showed a magnitude of insulin secretion in response to a 20-hour dextrose infusion and AIR to arginine stimulation similar to the response observed in nondiabetic control and ketosis-resistant T2DM subjects.

A large body of evidence indicates that the majority of patients with KPDM display clinical, metabolic, and immunological features of type 2 diabetes mellitus, are able to discontinue insulin therapy in 2-3 months and remain in normoglycemic remission for months to several years (1-3; 5; 6). Previous work demonstrated that at presentation patients with KPDM have no insulin response to glucose, however during remission such patients are able to produce insulin in response to intravenous glucose similar to non-diabetic subjects (5; 7). In addition, the resolution of hyperglycemia after 10-12 weeks of insulin therapy results in improvement of peripheral insulin sensitivity. Hence, these studies suggested that KPDM patients who achieved near-normoglycemic remission may not have irreversible β-cell damage; rather, these patients that present with hyperglycemic crisis have only transient functional abnormalities of insulin secretion or β-cell “desensitization”.

Evidence has shown that the continuous exposure of β-cells to elevated glucose concentration impairs insulin production and, if high glucose persists long enough, lead to irreversible damage of β-cells, a concept called “glucotoxicity” (11). Though most evidence supporting the phenomenon of β-cell damage is born from in vitro and in vivo studies (17), the concept of pancreatic glucotoxicity is thought to underlie loss of insulin production in the progression of T2DM (18; 19). Intensive insulin treatment has been shown to provide long-term β-cell benefits not only in KPDM but also in the setting of initial therapy for T2DM. Weng et al. recently reported that one week of intensive insulin administration in newly diagnosed T2DM patients resulted in remission of diabetes in half of the patients after 1 year of follow-up (20). In our study, we tested whether prolonged glucose exposure in patients with KPDM at remission would result in β-cell dysfunction. We found that the patients with KPDM experience similar increases in insulin and C-peptide levels and in C-peptide/glucose ratio compared to control subjects during the 20-hour dextrose infusion (Fig. 2). In addition, control subjects and KPDM patients had comparable area under curve for glucose suggesting that insulin-mediated glucose disposal in KPDM at remission is similar to that observed in nondiabetic obese subjects.

In attempt to understand in vivo phenomenon of pancreatic glucotoxicity, β-cell responsiveness to prolonged dextrose infusion was studied previously on healthy subjects. In lean or overweight non-diabetic humans, the infusion of dextrose ranging up to 68 hours and resulting in sustained hyperglycemia at levels between 108 mg/dL to 170 mg/dL did not cause suppression of insulin secretion (14; 21; 22). Also, ex vivo incubation of human β-cells with medium containing 180 mg/dL revealed no signs of glucotoxicity (23). Boden et al., however, demonstrated that, in overweight subjects, insulin secretion did not fall until 68 hours of dextrose infusion that was associated with a blood glucose of 227 mg/dL (21). We do not know whether exposure to higher glucose concentrations would result in β-cell failure in KPDM patients.
The hyperglycemic potentiating effect of insulin response to arginine is a sensitive indicator of β-cell secretory capacity (18; 24). The patients with KPDM demonstrated an appropriate glucose potentiating effect in response to arginine injection (Table 2). We did not observe increases in insulin secretion in all studied groups in response to the second arginine infusion after 20-hour dextrose infusion (Table 2 and Fig. 1); however, we were not able to achieve a similar degree of hyperglycemia during the second arginine infusion. The ability of KPDM patients to appropriately increase insulin secretion to prolonged glucose infusion and during repeated arginine stimulation indicated a remarkable recovery of insulin secretion during near-normoglycemia remission. These results suggest that the patients with KPDM during remission have significant β-cell reserve to counteract the deleterious effect of short-term mild hyperglycemia.

Our study also indicates that patients with ketosis-resistant T2DM are more insulin resistant than the patients with KPDM. The surrogate marker of insulin resistance HOMA-IR was higher in the ketosis-resistant DM (Table 2), and BG levels were also higher during 20-hour dextrose infusion suggesting lower glucose utilization than in by control and KPDM subjects (Fig. 2). These findings are in accord with previous work by Garvey et al. (25). The authors demonstrated that, in poorly controlled patients with T2DM, an intensive insulin therapy for three weeks results in the improvement of β-cell function; however, despite improved glycemic control, patients will remain insulin resistant. Increased peripheral insulin resistance in KPDM and ketosis-resistant diabetics compared to healthy control subjects is also suggested by the lack of suppression of FFA during 20-hour dextrose infusion.

We acknowledge the following limitations in this study. We anticipated that the infusion of dextrose at 200 mg/m²/min for 20 hours (D10% at 250-300 ml/hr) would result in significant hyperglycemia in patients with a recent history of DKA and/or severe hyperglycemia. However, we observed only mild hyperglycemia that may not have been sufficient to impair β-cell responses. Higher dextrose infusion rate resulting in higher glucose concentration may be needed to achieve significant glucotoxicity (21). It is also feasible that the development of “glucotoxicity” requires the presence of elevated FFAs. In addition to inhibiting insulin action, recent evidence indicates that FFAs have an important role in regulation of β-cell function (11). Finally, our study included only African Americans, so the effect of prolonged dextrose infusion in KPDM subjects from different ethnic populations needs to be determined in future studies.

In summary, our studies demonstrate that, in the KPDM patients, near-normoglycemia remission is associated with a remarkable recovery in insulin secretion. Despite a recent history of severe hyperglycemia and ketoacidosis, KPDM patients in remission had similar basal and stimulated insulin secretion compared with obese healthy controls sufficient to prevent hyperglycemia during dextrose infusion.

ACKNOWLEDGEMENTS
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REFERENCES


Table 1. Clinical features of control subjects and subjects with ketosis-prone diabetes mellitus and ketosis-resistant type 2 diabetes mellitus presenting with hyperglycemia.

<table>
<thead>
<tr>
<th></th>
<th>Control (N=13)</th>
<th>Ketosis-prone DM (N=8)</th>
<th>Ketosis-resistant DM (N=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>40.0±9.3</td>
<td>42.8±10.6</td>
<td>49.7±8.1</td>
</tr>
<tr>
<td>Gender (M/F), n</td>
<td>1/12</td>
<td>6/2</td>
<td>5/2</td>
</tr>
<tr>
<td>Newly diagnosed DM, %</td>
<td>--</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Family history of DM, %</td>
<td>77</td>
<td>88</td>
<td>100</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>35.5±5.0</td>
<td>38.6±4.9</td>
<td>37.2±5.6</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>96.3±13.9</td>
<td>120.3±23.3</td>
<td>110.2±19.7</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>2.1±0.2</td>
<td>2.4±0.3</td>
<td>2.3±0.3</td>
</tr>
<tr>
<td>BG at presentation, mg/dL</td>
<td>90±9</td>
<td>712±342*</td>
<td>492±163*</td>
</tr>
<tr>
<td>HbA1c at presentation, %</td>
<td>--</td>
<td>12.1±3.6</td>
<td>13.0±2.3</td>
</tr>
<tr>
<td>Bicarbonate, mmol/L</td>
<td>--</td>
<td>14±4**</td>
<td>24±3</td>
</tr>
<tr>
<td>pH</td>
<td>--</td>
<td>7.20±0.22</td>
<td>7.37±0.04</td>
</tr>
<tr>
<td>Anion Gap, mmol/L</td>
<td>--</td>
<td>24.8±7.2*</td>
<td>12.8±5.4</td>
</tr>
<tr>
<td>β-hydroxybutyrate, mmol/L</td>
<td>--</td>
<td>6.3±3.0†</td>
<td>1.02±0.4</td>
</tr>
<tr>
<td>Time to remission, weeks</td>
<td>--</td>
<td>7.1±1.7</td>
<td>9.6±2.3</td>
</tr>
<tr>
<td>HbA1c at remission, %</td>
<td>--</td>
<td>5.9±0.3</td>
<td>6.4±1.1</td>
</tr>
<tr>
<td>BG at remission, mg/dL</td>
<td>--</td>
<td>95±9</td>
<td>104±18</td>
</tr>
</tbody>
</table>

Values are means±SD
* - p<0.01 vs control
** - p<0.05 vs ketosis-resistant DM
† - p<0.05 vs ketosis-resistant DM

Table 2. Metabolic characteristics of non-diabetic controls, ketosis-prone type 2 diabetes mellitus and ketosis-resistant type 2 diabetes mellitus a near-normoglycemia remission.

<table>
<thead>
<tr>
<th></th>
<th>Control (N=13)</th>
<th>Ketosis-Prone DM (N=8)</th>
<th>Ketosis-resistant DM (N=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>88±12</td>
<td>95±3</td>
<td>104±8*</td>
</tr>
<tr>
<td>Fasting insulin, μU/mL</td>
<td>10.7±1.7</td>
<td>16.0±4.5</td>
<td>15.8±3.0</td>
</tr>
<tr>
<td>Fasting C-peptide, ng/mL</td>
<td>2.3±0.6</td>
<td>2.7±0.6</td>
<td>2.7±0.6</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.3±0.4</td>
<td>3.6±1.0</td>
<td>4.0±0.8*</td>
</tr>
<tr>
<td>FFA, μmol/L</td>
<td>113±21</td>
<td>120±35</td>
<td>117±29</td>
</tr>
</tbody>
</table>

AIR and FPIR to Arginine stimulation and HOMA-IR-to-FPIR ratio before and after glucose infusion (200 mg/m²/min) for 20 hours

Before 20-hr glucose infusion
<table>
<thead>
<tr>
<th></th>
<th>Control (N=13)</th>
<th>Ketosis-Prone DM (N=8)</th>
<th>Ketosis-resistant DM (N=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-infusion AIR₁, μU/mL</td>
<td>31±6</td>
<td>39±14</td>
<td>52±23</td>
</tr>
<tr>
<td>FPIR, μU/mL</td>
<td>197±33</td>
<td>264±80</td>
<td>339±221</td>
</tr>
<tr>
<td>HOMA-IR-to-FPIR ratio</td>
<td>0.014±0.003</td>
<td>0.015±0.003</td>
<td>0.013±0.002</td>
</tr>
</tbody>
</table>

After 20-hr glucose infusion
<table>
<thead>
<tr>
<th></th>
<th>Control (N=13)</th>
<th>Ketosis-Prone DM (N=8)</th>
<th>Ketosis-resistant DM (N=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-infusion AIR₁, μU/mL</td>
<td>40±5</td>
<td>34±13</td>
<td>62±27</td>
</tr>
<tr>
<td>FPIR, μU/mL</td>
<td>299±30</td>
<td>359±42</td>
<td>381±147</td>
</tr>
<tr>
<td>HOMA-IR-to-FPIR ratio</td>
<td>0.010±0.002</td>
<td>0.012±0.005</td>
<td>0.013±0.005</td>
</tr>
</tbody>
</table>

AIR₁: acute insulin response following the first arginine pulse; FPIR: first phase insulin release to arginine, HOMA-IR: homeostasis model assessment of insulin resistance.
Values are means±SE. * - p<0.05 vs control
**Figure legends:**

**Figure 1.** Arginine stimulation tests performed prior to (A) and following a 20-hour Dextrose infusion (B) in control subjects, KPDM subjects, and ketosis-resistant DM subjects. A maximally stimulatory dose of 10% arginine (5 g) was injected at baseline plasma glucose and following an infusion of 10% Dextrose at 200 mg/m²/min for 45 minutes. BG – blood glucose in mg/dL. Values are mean ± SE.

**Figure 2.** Changes in blood glucose (A), insulin (B), C-peptide/glucose ratio (C) during 20-hour glucose infusion as 10% dextrose at 200 mg/m²/min in control subjects, KPDM subjects, and ketosis-resistant DM subjects one week after achieving near-normoglycemic remission. Values are mean ± SE.

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![Figure 1A](image1A.png)

**1A**

![Figure 1B](image1B.png)

**1B**
Fig 2

2A

Control → Ketosis-prone DM → Ketosis-resistant DM

Blood glucose (mg/dl)

0 2 4 6 8 10 12 14 16 18 20

Meal

2B

Insulin (μU/ml)

0 2 4 6 8 10 12 14 16 18 20

Meal

2C

C-peptide/glucose

0 0.02 0.04 0.06 0.08 0.1 0.12

0 2 4 6 8 10 12 14 16 18 20

Hours

β-cell function in KPDM